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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,477	09/24/2001	Yuji Ishihara	2001-1276	6807

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,477	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,17,20,26-30,35 and 36* is/are pending in the application.

4a) Of the above claim(s) *14-16,19,21-25 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,17,20,26-30,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07-13-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

Applicant's amendment of 06-30-04 has been fully considered. Applicant's argument has not been found persuasive for the reasons stated below. Therefore, all previous rejections are maintained herein.

Claim 18 has been cancelled.

Claims 14, 15, 16, 19, 21-25, and 31-34 have been withdrawn.

Claims 35 and 36 have been added. Therefore, pending claims are 1-13, 17, 20, 26-30, 35 and 36.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

1. Claims 1-13 and 17 stay rejected under 35 U.S.C. 112, **second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Although the limitation of $-(C=O)-OR^3$ has been deleted from the definition of *"acyl"*, other variables still have *"carbamoyl"* as a substitutent. For example, the definitions of R^2 and R^3 include: carbamoyl, mono-loweralkyl-carbamoyl, di-loweralkyl-carbamoyl, etc. Therefore, it appears that dependent claims are still inconsistent with the limitation of *"non-carbamate"* recited in claim 1.

2. Claim 17 stay rejected under 35 U.S.C. 112, **first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant asserts that "*combination therapy is well known in the art*", and cites two references to support applicant's argument for enablement. However, in the instant case, mixing the claimed AchE inhibitor with an α-blocker could be dangerous, and therefore, the skilled clinician would need explicit guidance. The two cited references do not support the enablement for claim 17 because they teach the combination of α-blocker with a *cholinergic* agent, and not with AchE inhibitor as claimed herein. Therefore, applicant's argument is simply not on point.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-3, 6-9, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kawakita et. al.** (US 5,864,039). As stated in the previous rejection, Kawakita et. al. disclose the following elements:

a. A method of treating dysuria (column 3), which would have to *improve excretory potency of an urinary bladder.*

b. Two compounds (column 18, lines 32 and 34) that fall within the scope of claims 1-3, 6-9 and 35.

c. Applicant argues that Kawakita's compounds are not AchE inhibitors, and therefore, cannot anticipate the above claims. However, said compounds treat dysuria which is the end result of *improving excretory potency of an urinary bladder*. Therefore, the inhibitory activity of AchE is inherent based on structural similarity.

d. If applicant denies the inherency for AchE inhibition based on structural similarity, then in essence, applicant denies the same activity for compounds claimed herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-13, 20, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gotto et. al.** (US 5,527,800) in view of **Tobin et. al.** (Eur. J. Pharm., (1995), Vol. 281, pp. 1-8), and further in view of **Lai et. al.** (Life Sciences, (1998), Vol. 62, No. 13, pp. 1179-1186). As indicate in the previous action, Goto et. al. disclose AchE inhibitors, many of which are peri-

fused tricyclic compounds (e.g., compounds #38-40 in Table 63) that fall within the formula recited in the instant claims 1-13, having the following substituents:

i. Ar is a condensed phenyl, or the peri-fused tricycle of rings (A-C'-(N)-D'), or more specifically, the ring of *pyrrolo[3,2,1-ij]quinolin-4-one;*

ii. Y is piperidinyl substituted with R^6;

iii. R^6 is an optionally substituted C_7-aralkyl group;

iv. and n = 2;

In fact, the first compound of the instant claim 13 is actually compound #40 of Goto et. al., and the second compound of the instant claim 13 is actually compound #38 of Goto et.al. Both compounds of Goto et. al. can inhibit cholinesterase as indicated in Table 76 of US'800, column 230. Although Goto et. al. does not use their compounds for "*improving excretory potency of urinary bladder*", the teachings of Tobin et. al. and Lai et. al. would motivation for one skilled in the art to use Goto's compounds for such an application.

Tobin et. al. identify three acetylcholine (or muscarinic) receptors: M_1, M_2, and M_3 that affect a bladder. Lai et. al. further reveal that *"activation of M_2 receptor indirectly contributes to bladder contraction..."* Therefore, based on the teachings of Tobin et. al. and Lai et. al., one of the ordinary skill in the art would have been motivated to use Goto's compounds in treating bladder related disorder (including dysuria) because said compounds are cholinesterase inhibitors.

Applicant argued that contracting bladder muscle alone would not directly lead to an action of "improving excretion potency of bladder". Applicant even cited distigmine which

could contract the bladder and the urethra, which in turn would not improve the urinary efficiency. However, Goto's compounds are **not** distigmine's analogs. They are the same compounds recited in the instant claim 13, and are also cholinesterase inhibitors. With the relationship of acetylcholine receptors and bladder's contraction found by Tobin et. al. and Lai et. al., it would have been obvious for one skilled in the art to apply Goto's compounds to "improve excretion potency of bladder".

5. Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gotto et. al.** (US 5,527,800). Claims 26-28 are drawn to crystals of 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof. Claim 29 is drawn to the pharmaceutical composition of said crystals. Claim 30 is drawn to an acetylcholineserase inhibitor comprising the pharmaceutical composition of claim 29. The teaching of Gotto et. al. discloses a closely analogous crystalline compound (see compound #40). The disclosed crystal also inhibits acetylcholinesterase. Therefore, it would have been obvious for one skilled in the art to make the claimed crystal and incorporate it in pharmaceutical composition.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 703-305-4485. The examiner can normally be reached on M-F (9:30-5:00) & every other weekend (fom 3-15).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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11-12-04

Tamthom N. Truong
Examiner
Art Unit 1624

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